

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 18 June 1999 (18.06.99)	
<b>International application No.</b> PCT/US98/14776	<b>Applicant's or agent's file reference</b> DSI-10052/22
<b>International filing date</b> (day/month/year) 16 July 1998 (16.07.98)	<b>Priority date</b> (day/month/year) 16 July 1997 (16.07.97)
<b>Applicant</b> GESTER, Thomas, E. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
16 February 1999 (16.02.99)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

R. Forax

Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

<b>To: ELLEN S. COGAN</b> GIFFORD, KRASS, GROH, SPRINKLE & PATMORE 280 N. OLD WOODWARD AVE. STE. 400 BIRMINGHAM, MI 48009-5394  <i>DWS/ESC</i>
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## PCT

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference DSI-10052/22	Date of Mailing (day/month/year)
International application No. PCT/US98/14776	International filing date (day/month/year) 16 JULY 1998
Applicant DIVERSIFIED SCIENTIFIC, INC.	

*Response out 11-19-98  
due 12-19-98*

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.  
**Filing of amendments and statement under Article 19:**  
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):  

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.  
  
**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35  
  
 For more detailed instructions, see the notes on the accompanying sheet.
  
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
  
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
 

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.  
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
  
4. **Further action(s):** The applicant is reminded of the following:  
 Shortly after 18 months from the priority date, the international application will be published by the International Bureau.  
 If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.  
  
 Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).  
  
 Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230	Authorized officer ANDREW W. JOHNS  Telephone No. (703) 305-3900
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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DSI-10052/22	<div style="display: flex; justify-content: space-between;"> <div> <b>FOR FURTHER ACTION</b> </div> <div> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small> </div> </div>	
International application No. PCT/US98/14776	International filing date ( <i>day/month/year</i> ) 16 JULY 1998	(Earliest) Priority Date ( <i>day/month/year</i> ) 16 JULY 1997
Applicant DIVERSIFIED SCIENTIFIC, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (See Box I).
  
2. ☐ Unity of invention is lacking (See Box II).
  
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 

☐ filed with the international application.  
☐ furnished by the applicant separately from the international application,  

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ transcribed by this Authority.
  
4. With regard to the title,
 

☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:
  
5. With regard to the abstract,
 

☐ the text is approved as submitted by the applicant.  
☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
  
6. The figure of the drawings to be published with the abstract is:  
 Figure No. 1

☒ as suggested by the applicant.
 

☐ None of the figures.

☐ because the applicant failed to suggest a figure.  
☐ because this figure better characterizes the invention.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

## NEW ABSTRACT

A system utilizing a digital computer for acquiring, storing and evaluating crystal images. The system includes a video camera (12) which produces a digital output signal representative of a crystal specimen positioned within its focal window (16). The digitized output from the camera (12) is then stored on data storage media (32) together with other parameters inputted by a technician and relevant to the crystal specimen. Preferably, the digitized images are stored on removable media (32) while the parameters for different crystal specimens are maintained in a database (40) with indices to the digitized optical images on the other data storage media (32). Computer software is then utilized to identify not only the presence and number of crystals and the edges of the crystal specimens from the optical image, but to also rate the crystal specimens by various parameters, such as edge straightness, polygon formation, aspect ratio, surface clarity, crystal cracks and other defects or lack thereof, and other parameters relevant to the quality of the crystals.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/14776

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :G06K 9/00

US CL :382/100

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 382/100, 108, 109; 356/30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,544,254 A (HARTLEY et al.) 06 August 1996; column 4, line 52 through column 5, line 11; column 5, lines 21-27; column 5, line 44 through column 6, line 10.	1-5
X	US 5,076,698 A (SMITH et al.) 31 December 1991; column 1, line 64 through column 2, line 40.	1-5
A	US 5,193,685 A (TREVITHICK) 16 March 1993; see the entire document.	1-5
A	US 5,124,935 A (WALLNER et al.) 23 June 1992; see the entire document.	1-5
A	US 4,900,147 A (BOWLEY et al.) 13 February 1990; see the entire document.	1-5

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

\* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*&amp;\*

document member of the same patent family

Date of the actual completion of the international search

16 SEPTEMBER 1998

Date of mailing of the international search report

19 OCT 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20531

Authorized officer

ANDREW W. JOHNS



From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: ELLEN S. COGAN  
GIFFORD, KRASS, GROH, SPRINKLE & PATMORE  
280 N. OLD WOODWARD AVE.  
STE. 400  
BIRMINGHAM, MI 48009-5394

**PCT**

NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing  
(day/month/year)

**23 SEP 1999**

Applicant's or agent's file reference

DSI-10052/22

**IMPORTANT NOTIFICATION**

International application No.

PCT/US98/14776

International filing date (day/month/year)

16 JULY 1998

Priority Date (day/month/year)

16 JULY 1997

Applicant

DIVERSIFIED SCIENTIFIC, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

**RECEIVED**  
**SEP 27 1999**

GIFFORD, KRASS, GROH, SPRINKLE,  
ANDERSON & CITKOWSKI, P.C.

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ANDREW W. JOHNS

Telephone No. (703) 305-3900

## PATENT COOPERATION TREATY

PCT

RECD 20 SEP 1999

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DSI-10052/22	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/14776	International filing date (day/month/year) 16 JULY 1998	Priority date (day/month/year) 16 JULY 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): G06K 9/00 and US Cl.: 382/100		
Applicant DIVERSIFIED SCIENTIFIC, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 16 FEBRUARY 1999	Date of completion of this report 03 SEPTEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ANDREW W. JOHNS <i>For Virginia Zapp</i> Telephone No. (703) 305-3900

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14776

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

☐ the international application as originally filed.

☒ the description, pages (See Attached) , as originally filed.

pages \_\_\_\_\_ , filed with the demand.

pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. (See Attached) , as originally filed.

Nos. \_\_\_\_\_ , as amended under Article 19.

Nos. \_\_\_\_\_ , filed with the demand.

Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/~~fig~~ (See Attached) , as originally filed.

sheets/~~fig~~ \_\_\_\_\_ , filed with the demand.

sheets/~~fig~~ \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

sheets/~~fig~~ \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE .

☒ the claims, Nos. 2-4, 10 and 14 .

☒ the drawings, sheets/~~fig~~ NONE .

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14776

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1, 5-9 and 11-13</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1, 5-9 and 11-13</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-14</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1, 5-9 and 11-13 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the various additional features now stipulated in these claims. Claim 1 has been amended to include the limitations of cancelled claims 3-4 and 14. Claims 6, 11 and 13 have been amended to incorporate the limitations of the independent claim. Each of these claims includes limitations not taught or fairly suggested by any of the prior art. Claims 5, 7-9 and 12 are variously dependent from these independent claims and are also not taught or fairly suggested by the prior art.

----- NEW CITATIONS -----  
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14776

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**I. BASIS OF REPORT:**

This report has been drawn on the basis of the description,  
pages, 2-15, as originally filed.  
pages, 1 and 1A, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the claims,  
numbers, NONE, as originally filed.  
numbers, NONE, as amended under Article 19.  
numbers, NONE, filed with the demand.  
and additional amendments:  
Claims 1, 5-9 and 11-13 filed with the letter of 20 July 1999.

This report has been drawn on the basis of the drawings,  
sheets, 1-3, as originally filed.  
sheets, NONE, filed with the demand.  
and additional amendments:  
NONE

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/14776

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :G06K 9/00

US CL :382/100

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 382/100, 108, 109; 356/30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,544,254 A (HARTLEY et al.) 06 August 1996; column 4, line 52 through column 5, line 11; column 5, lines 21-27; column 5, line 44 through column 6, line 10.	1-5
X	US 5,076,698 A (SMITH et al.) 31 December 1991; column 1, line 64 through column 2, line 40.	1-5
A	US 5,193,685 A (TREVITHICK) 16 March 1993; see the entire document.	1-5
A	US 5,124,935 A (WALLNER et al.) 23 June 1992; see the entire document.	1-5
A	US 4,900,147 A (BOWLEY et al.) 13 February 1990; see the entire document.	1-5

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

16 SEPTEMBER 1998

Date of mailing of the international search report

19 OCT 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ANDREW W. JOHNS

Telephone No. (703) 305-3900

The block diagram illustrates a video microscope system 10. At the center is a CPU 24, which includes an internal HD (Hard Drive) 40. The CPU 24 is connected to several components: a DISPLAY 36, a VIDEO CARD 28, a VIDEO CAMERA 12, a MOTORIZED MECHANISM 20, and a FIBER OPTIC LIGHTING SYSTEM 30. A KEYBOARD 34 is connected to the CPU 24. DATA STORAGE 32 is connected to the CPU 24 and the MOTORIZED MECHANISM 20. The VIDEO CAMERA 12 is connected to the CPU 24 and the OPTICS 16. The OPTICS 16 is connected to the LCVR 18, which is connected to the TRAY 14. The TRAY 14 is connected to the MOVABLE STAGE 16, which is connected to the FIBER OPTIC LIGHTING SYSTEM 30. The FIBER OPTIC LIGHTING SYSTEM 30 is connected to the MOTORIZED MECHANISM 20. The MOTORIZED MECHANISM 20 is connected to the CPU 24 and the DATA STORAGE 32. The VIDEO CARD 28 is connected to the CPU 24 and the DISPLAY 36. The DISPLAY 36 is connected to the CPU 24. The KEYBOARD 34 is connected to the CPU 24. The DATA STORAGE 32 is connected to the CPU 24 and the MOTORIZED MECHANISM 20. The VIDEO CAMERA 12 is connected to the CPU 24 and the OPTICS 16. The OPTICS 16 is connected to the LCVR 18, which is connected to the TRAY 14. The TRAY 14 is connected to the MOVABLE STAGE 16, which is connected to the FIBER OPTIC LIGHTING SYSTEM 30. The FIBER OPTIC LIGHTING SYSTEM 30 is connected to the MOTORIZED MECHANISM 20. The MOTORIZED MECHANISM 20 is connected to the CPU 24 and the DATA STORAGE 32.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
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CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
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EE	Estonia	LR	Liberia	SG	Singapore		

## **METHOD FOR ACQUIRING, STORING AND ANALYZING CRYSTAL IMAGES**

### **Background of the Invention**

#### **I. Field of the Invention**

5           The present invention relates to a computer controlled system which acquires, stores and analyzes crystal images and other parameters relevant to the crystals, or microscopic details of other specimens.

#### **II. Description of the Prior Art**

10           In many chemical, pharmaceutical and medical applications crystals, e.g. protein crystals, are grown in trays for subsequent evaluation by a lab technician or scientist (hereinafter collectively referred to as "technician"). In evaluating the crystals once grown, the lab technician examines the crystals under the microscope and then visually evaluates or rates individual crystals. The straightness of the crystal edges, size of the crystal, presence or absence of flaws in the crystal as well  
15           as other crystal parameters are used by the technician in his or her rating process. The technician may also maintain notes of other parameters, such as pH, crystal growing time, temperature, et cetera, which are relevant to the particular crystal.

20           In some instances, the technician will take and maintain a photograph of the particular crystal under examination. The photograph is then stored along with the notes relevant to the particular crystals in the particular tray.

          This previously known system for evaluating and rating crystals is disadvantageous for a number of reasons. Most prominently, the crystal evaluation and rating system is labor intensive and, thus, not only slow and expensive in labor costs, but also tedious for the technician.

25           A still further disadvantage of these previously known systems is that the photographic record used for the examined crystal is expensive in material costs from the photographic process. Furthermore, photographs by their very nature are easily damaged and also deteriorate over time.

30           A still further disadvantage of the previously known method for evaluating and rating crystals is that no efficient means or system has been previously known for cross-referencing the various crystals and crystal parameters relative to each

other. Instead, the photographic picture as well as the other parameters relevant to the particular picture are simply maintained separately from the crystal specimens.

#### Summary of the Present Invention

5           The present invention provides a system utilizing a digital computer which overcomes all of the above-mentioned disadvantages of acquiring, storing and evaluating crystals, such as protein crystals, or microscopic details of other specimens.

10           In brief, the present invention utilizes a video camera which provides a digital output signal representative of an object, in this case crystals maintained within a tray, positioned within its focal window. Preferably, a central computer controls a movable stage to sequentially position trays in the focal window. The camera is operated under the control of a central computer which not only activates the initiation of the image acquisition by the camera, but also stores the  
15           output from the camera in digital form on data storage media. Preferably, the optical image from the video camera is stored on removable data storage media, such as a JAZZ™ drive, ZIP™ drive or CD ROM, etc..

20           In addition to storing the acquired optical image from the video camera, the technician, via a computer keyboard, mouse or other computer input means, also inputs data corresponding to parameters relevant to the particular crystal specimen under examination. Such parameters can include, for example, the pH, temperature, duration of crystal growth, et cetera for the particular crystal specimen. Additionally, the computer software preferably provides input template configurations to simplify the data input of the parameters by the technician and  
25           thus avoid or at least minimize the redundant input of information for different trays having similar parameters.

30           The various stored parameters may also be stored with the optical image on the data storage media. However, more preferably, the parameters relevant to the crystal specimens are stored in a database on one data storage media, for example a hard drive, with an index or record pointer to the appropriate image stored on the removable drive with the optical images. In this fashion, a large

4


database of the various crystal parameters may be maintained and analyzed relative to each other with access to the optical images always available as required or desired.

5 Following acquisition of the optical image as well as the other crystal parameters, the computer is programmed to analyze the optical image for the presence and count of protein crystals. As a part of the evaluation, the computer program identifies the edges of the crystal, filling in any gaps of the edge where necessary, and then analyzes the resulting data for its perimeter symmetry and roughness, straightness, crystal size, presence or absence of defects and center of gravity. The crystal rating is then stored in the data base.

10 Preferably, the present invention utilizes a fast T-squared filter during its analysis of the optical image in order to grade the crystal. Alternatively, the present invention utilizes a 3x3 edge detection filter during its analysis of the optical image in order to identify the crystal edges, then the image is converted to a binary image with a threshold of approximately 40 on a scale of 0 to 255 to reduce image artifacts. The size of the crystal is determined via perimeter connectivity analysis. Objects with a small perimeter are excluded. The net resulting image is analyzed for its roughness which is a measure of the perimeter divided by the convex perimeter. This metric is used to isolate the crystal from the drop boundary and other artifacts. The center of gravity is calculated on the remaining data to pinpoint the crystals.

15 Alternatively, other methods may also be used to grade the crystal based upon metrics such as edge straightness, aspect ratio, surface clarity, polygon formation, color etc. These methods include the use of traditional spatial filters such as highpass, lowpass, Butterworth, homomorphic, Sobel, Laplacian, etc. Probabilistic restoration such as least mean square (Wiener) filters, fast T-squared filters, spatial transformations, frequency transformations, etc. can be used. Edge linking and boundary detection using Hough Transforms, "Line-filler" filters, thresholding, etc. can be used. Representation and description using Fourier descriptors, topological descriptors, texture descriptors, statistical descriptors, moments, mathematical morphological descriptors, etc. can be used. Recognition

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using minimum distance classifiers, correlation classifiers, statistical classifiers, Bayesian classifiers, neural networks, genetic algorithms, etc. can be used.

### Brief Description of the Drawing

5 A better understanding of the present invention will be had upon reference to the following detailed description when read in conjunction with the accompanying drawing, wherein like reference characters refer to like parts throughout the several views, and in which:

FIG. 1 is a block diagrammatic view illustrating a preferred embodiment of the present invention;

10 FIG. 2 is an exemplary image of a crystal; and

FIGS. 3 through 6 are flow charts illustrating the operation of the system of the present invention.

### Detailed Description of a Preferred Embodiment of the Present Invention

15 With reference first to FIG. 1, a block diagrammatic view of a preferred embodiment of the system of the present invention is there shown and comprises a video camera 12 which, upon activation, generates a signal on its output line 10 representative of the optical image in its focal window 16. A tray 18 containing the crystals under examination is positioned within the focal window 16.

20 Although the tray 18 can be positioned manually within the focal window 16 of the camera 12, in the preferred embodiment of the invention, preferably a plurality of trays 18, e.g. two trays, are positioned on a movable stage at a time and each tray contains twenty-four to ninety-six wells while a motorized mechanism 20 is used to control the position of the stage 22. A central processing  
25 unit or computer 24, under program control, then controls the activation of the motorized mechanism 20 by generating appropriate signals on line 25 and thus controls the position of the stage 22. In doing so, the motorized mechanism 20 automatically sequentially positions the individual wells 18 within the focal window 16 of the camera 12 so that an optical image of each well 18 is acquired.

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A1  
CDN  
least minimize, the entry of redundant or repetitive information by the technician. Examples of such are included in Appendix A, incorporated herein.

The various parameters for each crystal specimen are also stored on data storage media, such as a hard drive 40, in a database and preferably in a relational database. Since the various parameters pertinent to the crystal specimens consume considerably less storage space than the optical images themselves, preferably the parameters are stored on the hard drive 40 separate from the optical images stored by the data storage device 32. In doing so, the parameters stored on the hard drive 40 would include an index or pointer to the optical images stored by the data storage media unit 32 so that the various crystal parameters stored in the database may be easily correlated whenever desired to the optical images.

The storage of the optical images of the crystals on data storage media as well as the storage of the crystal parameters in a database, such as a relational database, provide substantial advantages over the previously known photography and handwritten notes currently utilized by technicians. Perhaps most importantly, the use of a relational database allows the data to be analyzed, sorted, correlated and otherwise manipulated under software control by the central processing unit 24. The storage of the optical images on data storage media also provides a permanent record of the images without the previously known degradation and possible damage of photographs.

With reference now to FIG. 2, an exemplary image of a crystal stored by the central processing unit on data storage media is there shown. The crystal includes a plurality of edges 152 having a certain degree of straightness. Additionally, the edges 152 of the image of the crystal 150 may include gaps 154 due to lighting deficiencies during the image acquisition, deficiencies of the camera 12, or for other reasons.

With reference now to FIG. 3, a flow chart illustrating the operation of the present invention is there shown. At step 50, the program is initialized and the central processing unit 24 generates signals on its output line 25 to the motorized mechanism 20 (FIG. 1) in order to move the stage 22 to position the first crystal tray well 18 within the focal window 16 of the video camera 12. Step 50 then branches to step 52. At step 52, the central processing unit 24 generates an output

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signal on line 26 to activate the video camera 12 to acquire the optical image and to input the optical image from the camera output line 10 of the camera 12 to the central processing unit 24. Step 52 then branches to step 54.

5 At step 54, the central processing unit 24 stores the optical image via the data storage device 32 (FIG. 1). Optionally, appropriate data compression software may be utilized to minimize the storage required by the optical image of the crystal storage. Likewise, optionally digital filtering algorithms may be also utilized to remove extraneous noise and otherwise enhance the digital image prior to storage on the data storage media by the storage device 32 or 40.

10 Concurrently with storing the optical image of the crystal on data storage media, the technician inputs various relevant parameters, such as pH, temperature, crystal growth duration, protein type, et cetera pertinent to the crystal under examination via the keyboard 34 or other input device. Preferably, the central processing unit 24 under software control provides appropriate templates to the technician replicating various parameters common to the various specimens in the trays 18 on the stage 22. In doing so, the entry of redundant or duplicative information by the technician between crystal specimens is minimized which minimizes not only the labor required from the lab technician, but also the entry of errors through human technician error.

15 20 The various crystal parameters entered by the technician are also stored at step 54 by the central processing unit 24 on the data storage media 32 or 40 (FIG. 1). Stored concurrently with the crystal parameters on the data storage media 32 or 40 is an index or pointer which correlates the stored crystal parameters to the stored image on data storage media by the data storage device 32.

25 30 Step 54 then branches to step 56 whereupon the central processing unit 24 generates output signals on its output line 25 to activate the motorized staged mechanism 20 to move the stage 22 to position the next well in the focal window 16 of the camera 12. Step 56 then branches to step 52 where steps 52 and 54 are reiteratively executed until an optical image and crystal parameters for each of the wells 18 on the stage 22 have been acquired and stored as previously described.

With reference now to FIGS. 4 and 5, following the acquisition and storage of the images and crystal parameters, step 58 is then executed to analyze the stored image. Step 58 is illustrated in greater detail in FIG. 5 and FIG. 6.

5 With reference then to FIG. 5, during the analysis of the stored image, the program at step 60 executes a fast T-squared filter in order to locate and identify the edges of the crystal image. The fast T-squared filter is essentially a local digital filter which looks for a line defined as a set of co-linear pixels having a mean value different from the mean value of adjacent pixels on both sides of the line. Preferably, the fast T-squared filter at step 60 computes the two sample T-  
10 statistic with a null value of 0.

Preferably, the T-squared filter utilizes integer mathematics to minimize computing time required by the central processing unit. The T-squared filter at step 60 is also preferably a variable width T-filter which identifies lines having variable widths, e.g. a width varying in size from one pixel to five pixels. Step 60  
15 then branches to step 62.

At step 62 a low pass filter is applied to the image to remove extraneous noise. Step 62 then branches to step 64.

At step 64, the program "fills" digitally any gaps, such as the gap 54 in FIG. 2, which may be present in the digitized image. Thus, following step 64, the  
20 program has identified not only the lines of the crystal, but also eliminated extraneous noise in the crystal image as well as completed any missing segments of the crystal edges due to deficiency of the camera, lighting or the like. Step 64 then branches to step 66 (FIG. 4).

At step 66, the program "scores" or evaluates the crystal images and then  
25 stores the score or evaluation as one of the crystal parameters on the storage device 40. Such scoring includes examination and evaluation of the straightness of the crystal edges, the presence or absence of defects in the crystal, fractures in the crystal and the like.

30 With reference then to FIG. 6, during the analysis of the stored image, the computer is programmed to analyze the optical image for the presence and count of protein crystals. As a part of the evaluation, the computer program identifies

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the edges of the crystal and than analyzes the resulting data for its perimeter symmetry and roughness and center of gravity.

Preferably, the present invention utilizes a 3x3 edge detection filter during its analysis of the optical image in order to identify the crystal edges, then the  
5 image is converted to a binary image with a threshold of approximately 40 on a scale of 0 to 255 to reduce image artifacts. The size of the crystal is determined via perimeter connectivity analysis. Objects with a small perimeter are excluded. The net resulting image is analyzed for its roughness which is a measure of the perimeter divided by the convex perimeter. This metric is used to isolate the  
10 crystal from the drop boundary and other artifacts. The center of gravity is calculated on the remaining data to pinpoint the crystals.

From the foregoing, it can be seen that the present invention provides a system for the automatic acquisition, storage and evaluation of crystal specimens under computer control. The use of software templates by the operator to  
15 minimize the entry of duplicative or repetitive information further enhances not only the reliability of the data inputted into the system, but also minimizes technician labor.

A still further advantage of the present invention is the storage of the crystal parameters in a relational database which enables the manipulation and  
20 evaluation (i.e., experimental history, archiving, trend analysis, etc.) of the crystal parameters under computer control utilizing search and 3-D plotting capabilities. The storage of the crystal images in removable data storage media separate from the storage of the crystal parameters also ensures that a large number of crystal parameters can be stored in the relational database with access to the crystal  
25 images always available.

Having described our invention, however, many modifications thereto will be come apparent to those skilled in the art to which it pertains without deviation from the spirit of the invention as defined by the scope of the appended claims.

We claim:

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APPENDIX A

**Cystallix**

File Setup Run Video Database View

Score Date 891/30/97 1/13/97

Protein Lysozyme

Concn 20mg/ml Vol 2uL pH 4.7

Protein Buffer Sodium Acetate

Concn 20mM

Reservoir Buffer Sodium Acetate

Concn 20mM Vol 1000uL pH 5

Drop Additive Sodium Acetate

Concn 20mM Vol 2uL

Precip Agent NaCl

Concn 8% Concn mV

Tray Well Temp 3A1 22C 81

Live Freeze Adjust Save Repeat Delete Exit

Acquire Search Fillers Database Thumbnails Plot

Start Delphi 20 Delphi H Exploring LVView Pro Proj1027

9:49 AM

**View Database**

Index	Protein	Protein Concentration	Protein Volume	Protein pH	Protein Buffer
75	Lysozyme	36	2	4.7	Sodium Acetate
76	Lysozyme	36	2	4.7	Sodium Acetate
77	Lysozyme	36	2	4.7	Sodium Acetate
78	Lysozyme	36	2	4.7	Sodium Acetate
79	Lysozyme	36	2	4.7	Sodium Acetate
80	Lysozyme	36	2	4.7	Sodium Acetate
81	Lysozyme	36	2	4.7	Sodium Acetate
82	Lysozyme	36	2	4.7	Sodium Acetate

Score: 89 Tray: 3 Well: A6 Entry Date: 1/30/97 Temp: 22 Index: 79

Protein: Lysozyme Concentration: 36 mg/mL Volume: 2 uL pH: 4.7

Protein Buffer: Sodium Acetate Concentration: 20 mM

Reservoir Buffer: Sodium Acetate Concentration: 20 mM Volume: 1 uL pH: 5

Drops/Additive: Sodium Acetate Concentration: 20 mM

Precipitating Agent: NaCl Concentration: 8 % mM

Acquire: Search: Filters: Database: Thumbnails: Plot: Start: Delphi 2000: Delphi H: Exploring: View Pro: PKZ/Pos: Proj1027: 10:16 AM



View Database

Index	Protein	Protein Concentration	Protein Volume	Protein pH	Protein Buffer
2	Lysozyme	40	10	4.7	Sodium Acetate
3	Lysozyme	40	10	4.7	Sodium Acetate
4	Lysozyme	40	10	4.7	Sodium Acetate
5	Lysozyme	40	10	4.7	Sodium Acetate
6	Lysozyme	40	10	4.7	Sodium Acetate
7	Lysozyme	40	8	4.7	Sodium Acetate
8	Lysozyme	40	8	4.7	Sodium Acetate
9	Lysozyme	40	8	4.7	Sodium Acetate

Lysozyme

Concentration

40

Volume

10

pH

4.7

Protein Buffer

Sodium Acetate

Residual Buffer

Concentration

40

Volume

10

pH

4.7

Protein Buffer

Sodium Acetate

Diet Additive

Concentration

40

Volume

10

pH

4.7

Protein Buffer

Sodium Acetate

Preparation Agent

Concentration

40

Volume

10

pH

4.7

Protein Buffer

Sodium Acetate

Search

Files

Database

Protein Data

Search

Files

Database

Protein Data

Search

Files

Database

Protein Data

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Files

Database

Protein Data

00T090\*05629H60



007090" 06520460

New Template						Copy Template						Delete Template																							
A						B						C						D																	
1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6												
Protein						Concentration						Volume						pH						Notes											
albumin						55						66												Memo1											
Protein Buffer						ADA						Concentration						Volume						pH						Temperature					
MOPS						53																													
Reservoir Buffer						Sodium Acetate						Concentration						Volume						pH						Temperature					
Lithium Sulfate						Concentration						Volume						pH						Temperature											
Save						Reset						Close																							



**Threshold Video**

0

**Custom Filter**

-1	-1	-1
-1	8	-1
-1	-1	-1

**High Pass**

**Low Pass**

**Gaussian**

**Sobel 1**

**Sobel 2**

**3x3 Horiz**

**3x3 Vert**

**5x5 Horiz**

**5x5 Vert**

**Line Corr**

**Correlation**

Claims

- 1           1.     A system for utilizing a digital computer to evaluate microscopic  
2 details of specimens, e.g. crystals, comprising:  
3           a camera which generates an output signal representative of an image  
4 positioned in a focal plane of the camera,  
5           means for automatically positioning a specimen in said focal plane,  
6           means for acquiring and storing said output signal from said camera,  
7           means for evaluating said stored image from said camera and for  
8 generating a result signal representative thereof,  
9           means for outputting said result signal.
- 1           2.     The invention as defined in claim 1 wherein said evaluating means  
2 comprises means for determining presence of crystals.
- 1           3.     The invention as defined in claim 2 wherein said evaluating means  
2 further comprises means for determining the count of said crystals.
- 1           4.     The invention as defined in claim 1 and comprising means for  
2 generating three-dimensional surface plots of experimental data within a database.
- 1           5.     The invention as defined in claim 1 and comprising means for  
2 automatically controlling zoom and focus.

*Replaced by Article 34*

**AMENDED CLAIMS**

[received by the International Bureau on 11 December 1998 (11.12.98);  
original claims 1-5 amended; new claims 6-14 added (2 pages)]

1           1.     A system for utilizing a digital computer to evaluate microscopic  
2 details of specimens, e.g. crystals, comprising:  
3           a camera which generates an output signal representative of an image  
4 positioned in a focal plane of the camera,  
5           a tray which positions a specimen in said focal plane,  
6           a computer processing unit having a persistent storage device, which  
7 computer processing unit acquires said output signal from said camera,  
8           said computer processing unit being programmed to evaluate said stored  
9 image from said camera and for generating a result signal representative thereof,  
10          said computer processing unit being programmed to store said result  
11 signals in said persistent storage device.

1           2.     The invention as defined in claim 1 wherein each said specimen  
2 comprises at least one crystal.

1           3.     The invention as defined in claim 2 wherein said computer  
2 processing unit is programmed to count said crystals.

1           4.     The invention as defined in claim 2 wherein said computer  
2 processing unit is programmed to generate three-dimensional surface plots of  
3 crystals within a database.

1           5.     The invention as defined in claim 1 and comprising a movable  
2 stage for automatically positioning said specimens in said focal plane.

1           6.     The invention as defined in claim 2 and comprising a T-squared  
2 filter to identify said crystals in each said specimen.

1           7.     The invention as defined in claim 6 where said T-squared filter  
2 comprises a software program executed by said computer processing unit.

1           8.     The invention as defined in claim 5 wherein said computer  
2     processing unit generates output signals to control the movement of said movable  
3     stage.

1           9.     The invention as defined in claim 4 wherein data relating to said  
2     crystal(s) is stored in the database.

1           10.    The invention as defined in claim 1 and comprising a light source  
2     directed to said specimen.

1           11.    The invention as defined in claim 10 and comprising an optical  
2     fiber extending between said light source and said specimen.

1           12.    The invention as defined in claim 2 and comprising a computer  
2     algorithm executed by said computer processing unit for rating said crystals with  
3     respect to predetermined standards.

1           13.    The invention as defined in claim 2 and comprising a computer  
2     algorithm executed by said computer processing unit for simulating edges of  
3     crystals missing in said image generated by said camera.

1           14.    The invention as defined in claim 2 wherein said computer  
2     processing unit is programmed to determine crystal size by determination of the  
3     length of the perimeter of said crystals.